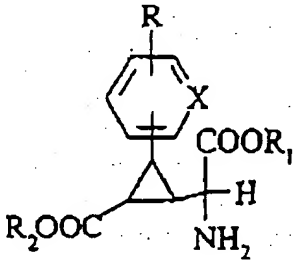


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<p>(21) International Application Number: PCT/EP96/05079 (22) International Filing Date: 18 November 1996 (18.11.96) (30) Priority Data: 95/A002383 17 November 1995 (17.11.95) IT (71) Applicant (for all designated States except AT DE US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (71) Applicant (for DE only): SANDOZ-PATENT-GMBH [DE/DE]; Humboldtstrasse 3, D-79539 Lorrach (DE). (71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienne (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): PELLICCIARI, Roberto [IT/IT]; Via U. Rocchi, 60, I-06123 Perugia (IT). MORONI, Flavio [IT/IT]; Via N. Machiavelli, 7, I-50125 Firenze (IT). KOLLER, Manuel [CH/CH]; Fuhrenstrasse 16, CH-3098 Schlieren (CH).</p>		<p>(74) Common Representative: NOVARTIS AG; Patents &amp; Trade-marks Division, Lichtstrasse 35, CH-4002 Basle (CH). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published With international search report.</p>
<p>(54) Title: GLYCINE DERIVATIVES</p> <p>(57) Abstract</p> <p>Compounds of formula (I), wherein R, R<sub>1</sub>, R<sub>2</sub> and X are as defined in the description, are useful as pharmaceuticals.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

## GLYCINE DERIVATIVES

The present invention relates to glycine derivatives with affinity to metabotropic glutamate receptors.

Metabotropic glutamate receptors (mGluR) are a family of proteins present in neurons and in the glia, which can interact with glutamate and bring about significant modifications in neurotransmission by interaction with protein G and the resulting regulation of the neosynthesis of second messengers or the modulation of ion channels both at the presynaptic and postsynaptic levels. Recent molecular biology studies have identified at least eight cDNAs which likewise code for mGluR subtypes. In general, on the basis of structural analogies, the effector used and pharmacological properties, it is possible to divide the eight mGluRs into three groups:

- 1st group: comprises mGluR1 and mGluR5 which are capable of stimulating phospholipase C and the inositol cycle. These receptors are stimulated by the antagonists in the following order of power: QUIS> 1S, 3R-ACPD>L-CCG1>>>>L-AP4.
- 2nd group: comprises mGluR2 and mGluR3 which are capable of inhibiting the formation of cAMP induced by forskolin. The order of power of the agonists is as follows: L-CCG1>1S,3R-ACPD>QUIS>>>>L-AP4.
- 3rd group: comprises mGluR4, mGluR6, mGluR7 and mGluR8 which are also capable of inhibiting the formation of cAMP, but in the following order of power: L-AP4>>1S,3R-ACPD>>>>L-CCG1.

The various mGluRs are differentially distributed in the CNS and several subtypes may coexist in the same area and also in the same neuron. The final effect their activation has depends on the types of receptor present and may therefore be either an inhibitory effect or an

excitatory effect. For example, in the cerebellum, the stimulation of mGluR1 leads to activation of the calcium-dependent potassium channels and therefore to inhibition, whereas, in the hippocampus, activation of mGluR receptors can increase the neuronal excitability by inhibiting the voltage-operated potassium channels. Then there are mGluRs which are localized to the presynaptic level and are capable of regulating the release of the transmitter by means of particularly interesting mechanisms. Thus, the stimulation of mGluR4 or mGluR7 can reduce the influx of  $Ca^{2+}$  into the nerve endings, thereby directly inhibiting the voltage-dependent channels and reducing the synaptic release of transmitter. A similar result can be obtained by stimulating the mGluR2 or mGluR3 receptors, which inhibit the formation of cAMP and in some way reducing the effects of depolarization on the release of the transmitter. In contrast, the stimulation of other mGluR subtypes (mGluR1 and possibly also mGluR5) amplifies the depolarization-release of transmitter combination, especially in the presence of free fatty acids.

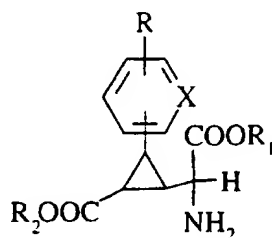
In light of the above, regulation of the functioning of mGluR-controlled neuronal circuits in the hippocampus becomes particularly advantageous. Stimulation of the mGluR4 and mGluR7 receptors reduces transmission at the glutamatergic synapses level, whereas stimulation of mGluR5 can increase the excitability of the circuit, possibly also because it amplifies responses of ionotropic type. The consequences of a reduction in transmission and an increase in excitability are that low-intensity stimuli are blocked, while strong stimuli, capable of overcoming the presynaptic inhibition, are amplified. In this way, the strategic location of the mGluRs leads to the formation of filtering systems capable of increasing the signal/noise ratio of the stimuli which converge on this neuronal circuit. Such systems, in which other types of mGluR also come into play, appear to operate both at the level of phenomena associated with learning and in regulating various

sensory signals (for example in the olfactory pathways). In the basal nuclei, the stimulation of mGluR2 and mGluR3 leads to a considerable reduction in the synaptic release of excitatory transmitter and may affect certain psychic and motor functions. Thus, the pharmacology of mGluRs appears to promise wide fields of therapeutic application since mGluRs appear to have an important role in the processes of neuroprotection and neurodegeneration, in controlling movement, and in the normal functioning of dopaminergic systems, in the onset of epileptic attacks, in the processes of central integration of pain, pressure, visual and sensory stimuli, and in learning. The fact that stimulation of the mGluR receptors can bring about an increase in the sensitivity of the ionotropic receptors for the same transmitter makes these receptors an ideal target for modifying synaptic excitatory functioning.

WO 93/08158 (Suntory Ltd.; 29.4.1993) describes enantiomers of 2-(2,3-dicarboxycyclopropyl)glycine as NMDA-receptor agonists and their therapeutic use as anaesthetics, analgesics and antispastic agents.

It has now been found that cyclopropylglycine derivatives are endowed with affinity to metabotropic glutamate receptors.

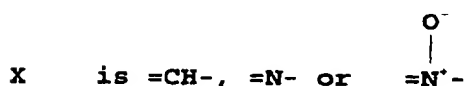
The compounds of the invention have the general formula (I) below



(I)

in which

- R is hydrogen, halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl, C<sub>1</sub>-C<sub>4</sub>haloalkoxy, cyano, nitro, -COOR<sub>1</sub> (R<sub>1</sub> being as defined below), -CONR<sub>2</sub>R<sub>3</sub> (R<sub>2</sub> and R<sub>3</sub> independently being hydrogen or C<sub>1</sub>-C<sub>4</sub>alkyl), -PO(OR<sub>1</sub>)<sub>2</sub> (R<sub>1</sub> being as defined below), -SO<sub>2</sub>R<sub>1</sub> (R<sub>1</sub> being as defined below) or -NH-CO-R<sub>5</sub> (R<sub>5</sub> being C<sub>1</sub>-C<sub>4</sub>alkyl or phenyl),
- R<sub>1</sub> and R<sub>2</sub>, independently, are hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl or benzyl, and



- The compounds of formula (I) have four asymmetric centres, which give rise to 16 enantiomers.

The invention comprises the individual enantiomeric forms as well as their racemic or diastereoisomeric mixtures.

- The invention moreover comprises the salts of the compounds (I) with acids or (when R<sub>1</sub> or R<sub>2</sub> = H) bases.

In a group of compounds of formula I, R is hydrogen, an halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl or C<sub>1</sub>-C<sub>4</sub>haloalkoxy, R<sub>1</sub> and R<sub>2</sub> are hydrogen and X is =CH- or =N- in ortho position to the bond which is linked to the cyclopropyl moiety.

Preferred compounds of formula (I) are those in which X is CH and R is hydrogen or a C<sub>1</sub>-C<sub>4</sub>alkoxy group.

- Examples of C<sub>1</sub>-C<sub>4</sub>alkyl groups include methyl, ethyl, n-propyl, isopropyl and isobutyl, preferably methyl.

Examples of C<sub>1</sub>-C<sub>4</sub>alkoxy groups include methoxy, ethoxy, n-propoxy and isopropoxy, preferably methoxy.

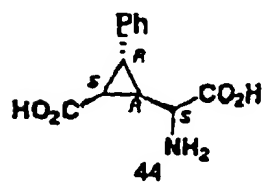
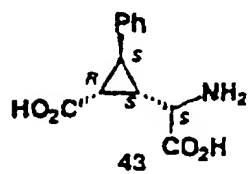
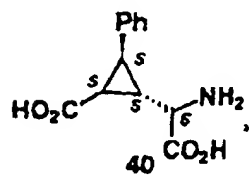
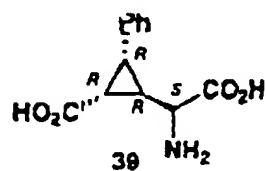
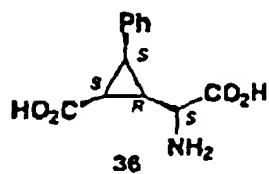
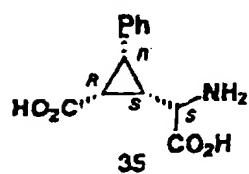
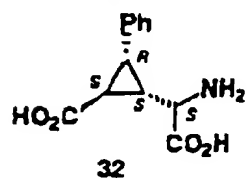
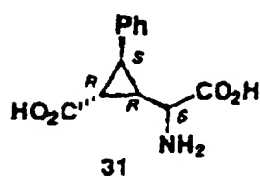
- Examples of C<sub>1</sub>-C<sub>4</sub>haloalkyl groups include trifluoromethyl and pentafluoroethyl, preferably trifluoromethyl.

Examples of C<sub>1</sub>-C<sub>4</sub>haloalkoxy groups include trifluoromethoxy and difluoromethoxy, preferably tri-

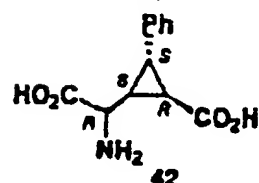
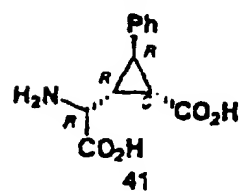
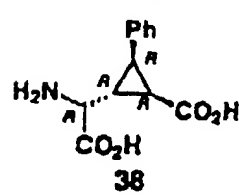
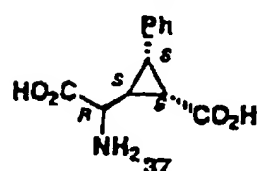
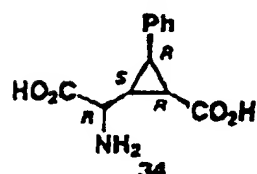
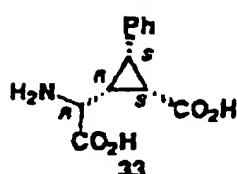
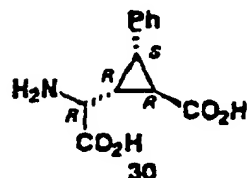
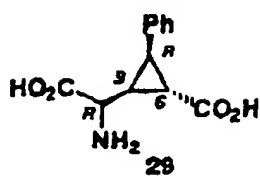
fluoromethoxy.

Th formulae of 16 possible enantiomers of the compounds of formula (I) in which R is H, X is =CH- and R<sub>1</sub> is hydrogen are given below. The S configuration of  
5 the carbon atom of the glycine residue is preferred and the configuration of compound 44 is particularly preferred.

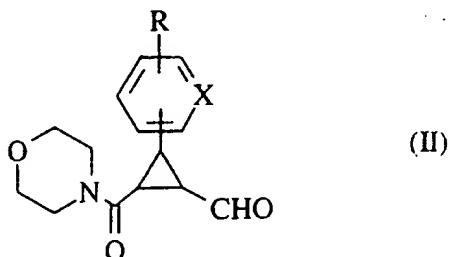
## S Series



## R Series



The compounds of formula I wherein  $R_1$  and  $R_2$  are H may be prepared by reaction of a compound of formula (II)



in which X and R are as defined above, with  $\alpha$ -phenylglycinol and then with TMSCN, followed by oxidative  
5 cleavage with lead tetraacetate and acid hydrolysis. The compounds wherein  $R_1$  and/or  $R_2$  are alkyl or benzyl can be prepared from the free acids according to well known procedures.

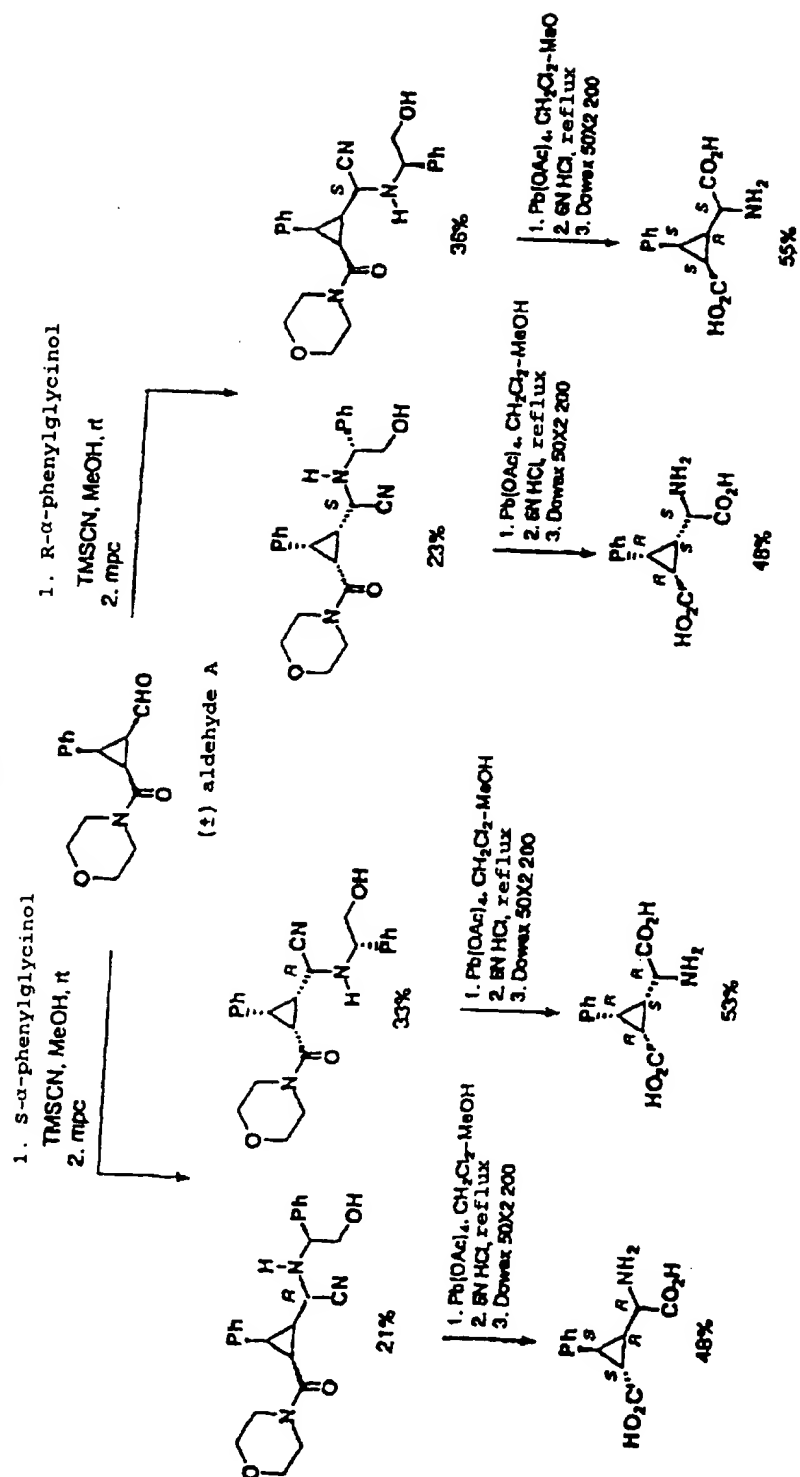
By using various enantiomers of the aldehydes (II)  
10 and of R- or S- $\alpha$ -phenylglycinol, the desired enantiomers may be prepared.

Schemes 1-4 for the preparation of compounds (I) in which X = CH and R = H are given below. Further compounds (I) can be obtained by identical methods, starting with  
15 appropriate aldehydes (II).

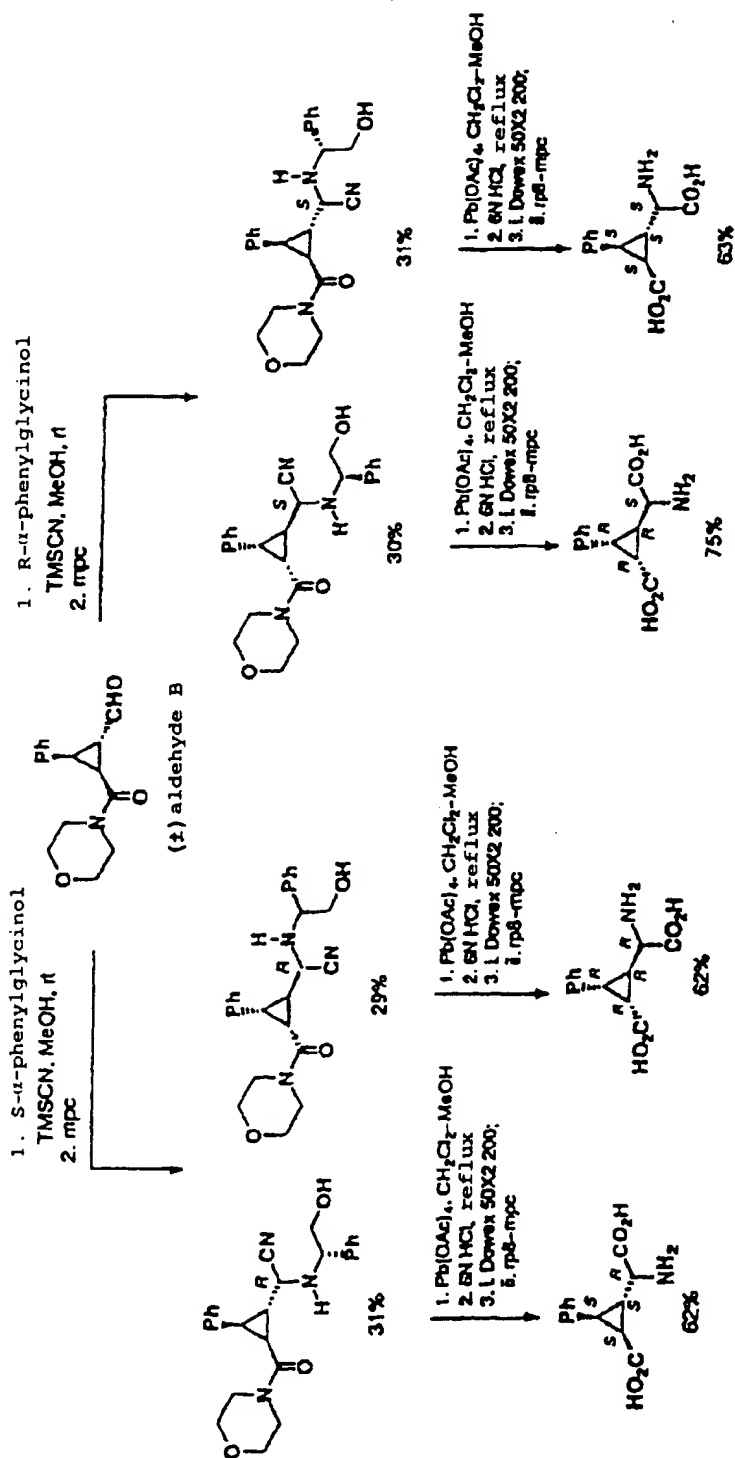
Aldehydes (II) can be prepared according to the following schemes 5 and 6, again with reference to compounds in which X is CH and R is hydrogen. Obviously, further aldehydes of formula (II) can be prepared in a  
20 similar manner, starting with the appropriate E-cinnamyl or E-pyridylvinyl alcohols.



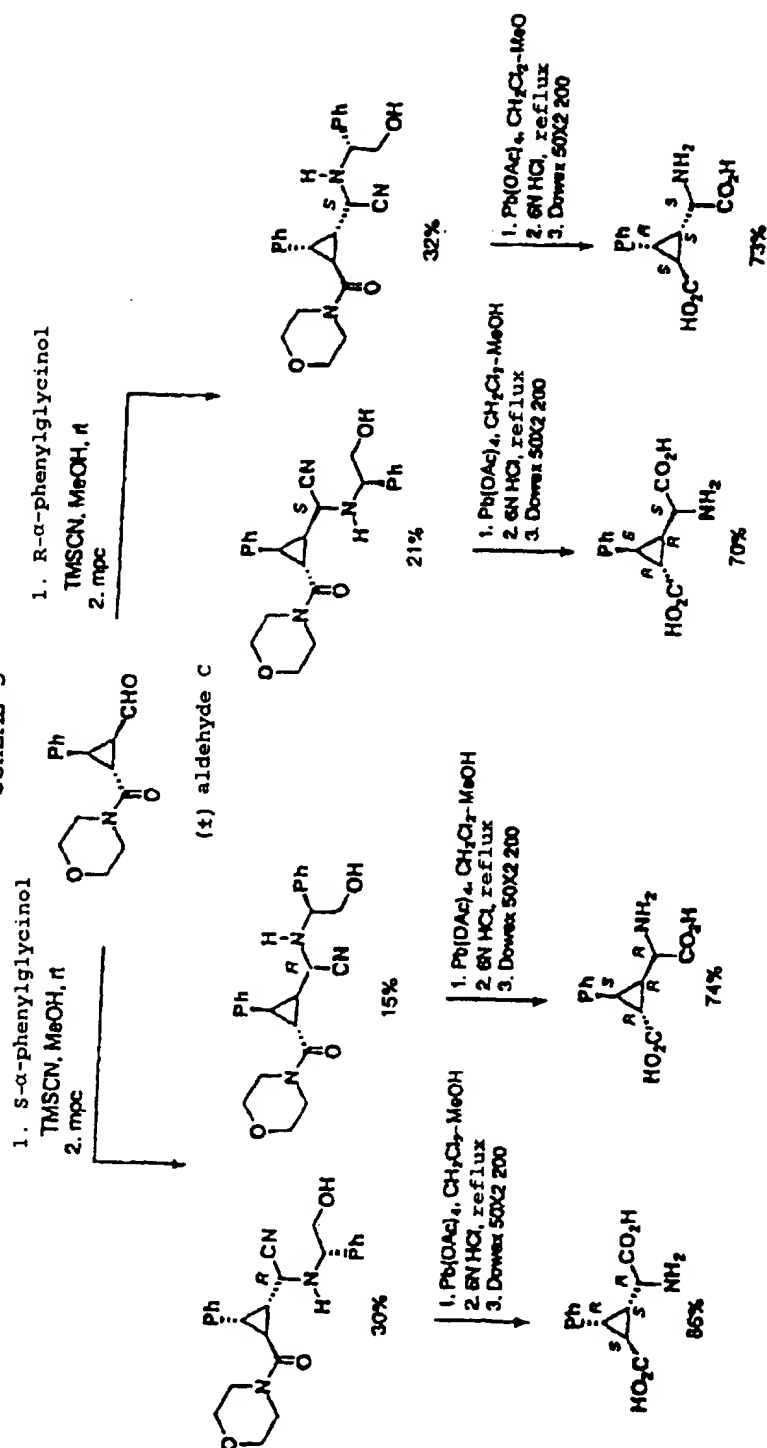
SCHEME 1



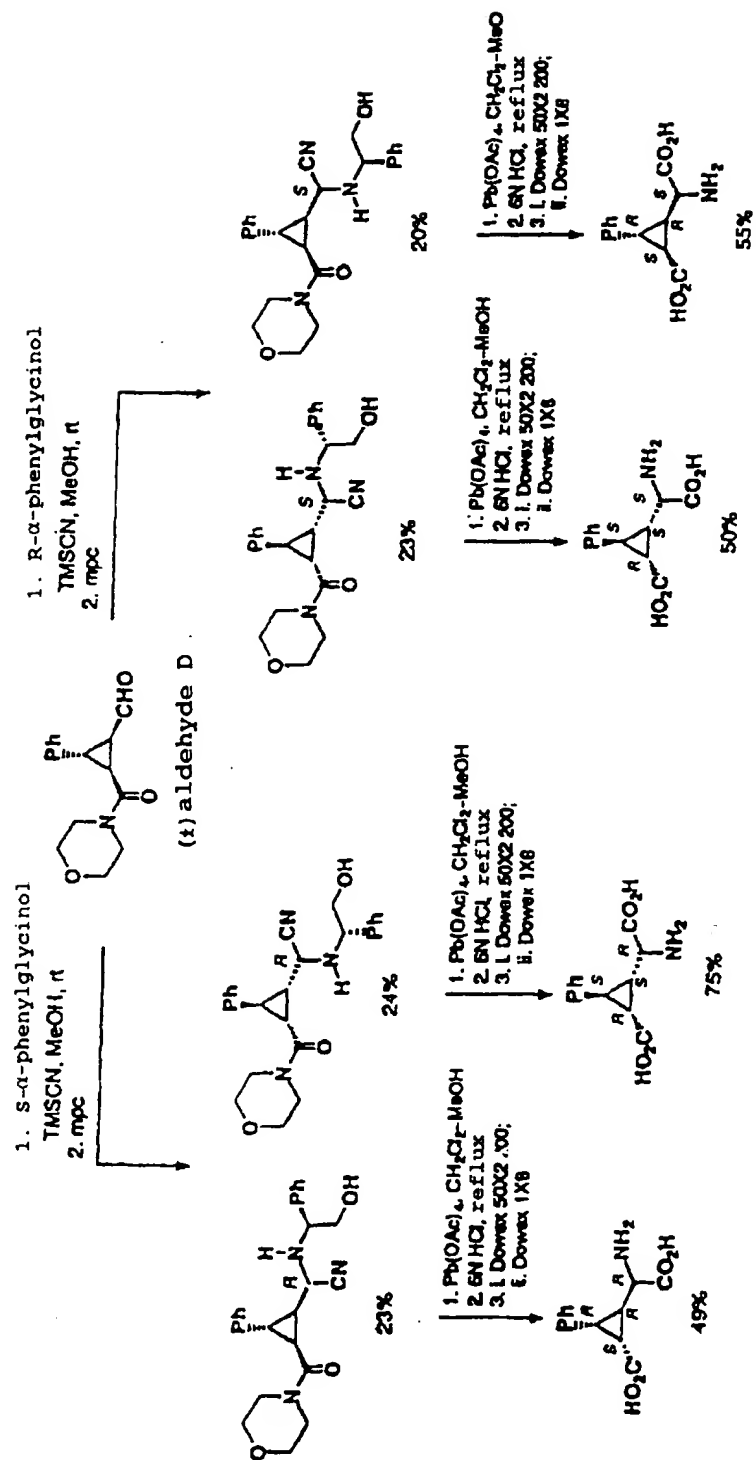
SCHEME 2

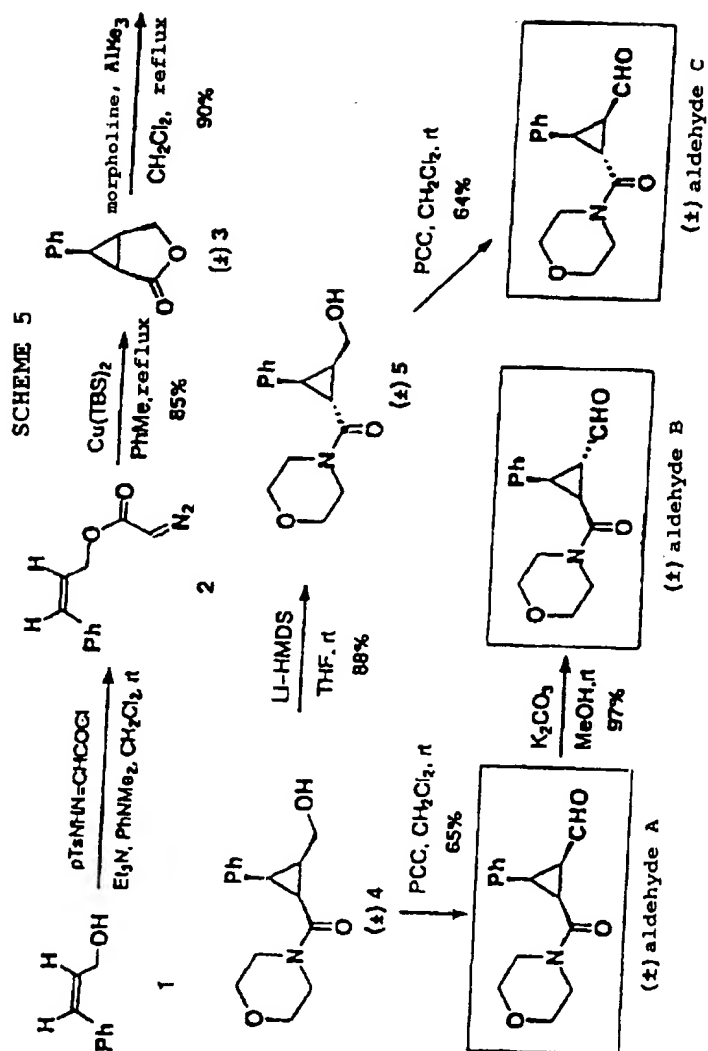


SCHEME 3

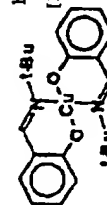


SCHEME 4



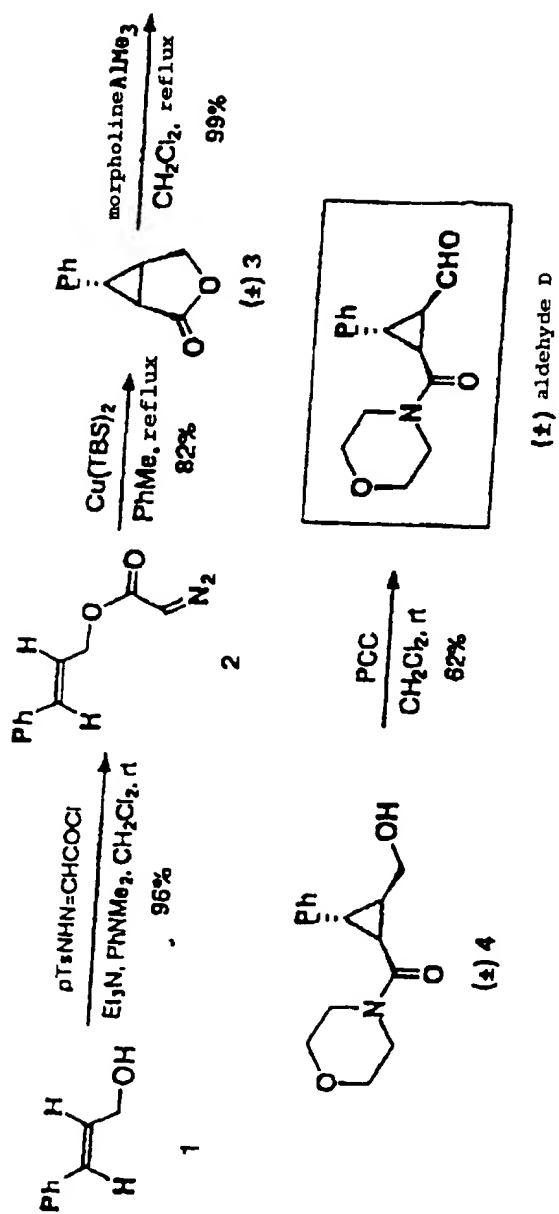


bis(N-t-Bu-salicylaldiminato)copper (II)  
 [E.J. Corey, et al., Tetrahedron Lett. 1984, 25, 3559]



$\text{Cu(TBS)}_2 =$

SCHEME 6



The compounds of formula (I) and their pharmaceutically acceptable salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro, particularly affinity to metabotropic glutamate receptors (mGluRs) as indicated above, and are therefore useful as pharmaceuticals.

The agents of the invention were evaluated as mGluR antagonists in the following tests:

- 1) Antagonism of the phospholipase C-stimulatory action by 1S,3R-ACPD (300  $\mu$ M) on slices of rat cortex. Active molecules in this test are considered to be mGluR1 or mGluR5 antagonists (group 1).
- 2) Antagonism of the action of L-CCG1 (3  $\mu$ M) on the formation of cAMP induced by forskolin (30  $\mu$ M) on slices of rat stria. Active molecules in this test are considered to be mGluR2 or mGluR3 antagonists (group 2).
- 3) Antagonism of the action of L-AP4 (10  $\mu$ M) on the formation of cAMP induced by forskolin (30  $\mu$ M) on slices of rat cerebellum. Active molecules in this test are considered to be mGluR4, mGluR7 and mGluR8 antagonists (group 3).

The agents of the invention show significant activity in these tests at about 0.01 to about 100 $\mu$ M.

The molecules active on group 1 mGluRs were then tested for their potentiation of the release of transmitter from slices of cortex and the molecules active on group 2 were tested for their inhibition of the release of transmitter from slices of rat stria. The methods used for the experiments reported above are described in: Lombardi et al. *British J. Pharmacol.* 1993, 110, 1407-1412.

The agents of the invention, and in particular compound 44, display selective antagonist activity towards the mGluRs of the second group by antagonizing the effect of L-CCG-1 on the production of cAMP and on the release of transmitter from slices of stria, with an  $IC_{50}$  of 10  $\mu$ M. The effect is selective since the action of

1S, 3R ACDP on phospholipase C is not modified.

Furthermore, the compounds of the invention may act as mGluR-agonists. Agonistic activity can be shown in the following way:

- 5 1) Stimulation of phospholipase C in BHK cells which are transfected with mGluRs of group I;
- 2) Decrease of forskolin-stimulated cAMP-formation in transfected BHK cells expressing one of the mGluRs of class II or III.

10 The agents of the invention show significant activity in these tests at about 0.01 to about 100µM. Compound 44, for example, acts as an agonist at mGluR4 with an EC50 < 200 µM.

The compounds of the invention are therefore  
15 useful in disorders which are linked to metabotropic excitatory amino acid receptors. Such disorders include cerebral ischemia (e.g. due to stroke or cardiac arrest during bypass surgery), head trauma, subarachnoid haemorrhage, Alzheimers disease, Huntingtons Chorea,  
20 amyotrophic lateral sclerosis, AIDS-induced dementia, Parkinson syndrom, convulsive disorders (e.g. epilepsy), muscular spasms, chronic and neuropathic pain, cognitive disorders such as memory deficits, schizophrenia, anxiety, emesis and drug abuse.

25 For the therapeutic uses envisaged, the compounds of the invention will be formulated in appropriate dosage forms, using conventional techniques and excipients. The dosage will be determined by the doctor in charge, based on the pharmaceutical and pharmacodynamic properties of  
30 the compounds. An indicated daily dosage will lie within the range from about 1 mg to about 1g, conveniently administered, for example, in divided doses up to four times a day.

In accordance with the foregoing, the present  
35 invention also provides a pharmaceutical composition comprising an agent of the invention, in association with a pharmaceutical carrier or diluent.

The invention furthermore provides an agent of the invention for use as a pharmaceutical, particularly



in disorders linked to metabotropic glutamate receptors, e.g. in the treatment of the above-mentioned disorders.

Moreover the present invention provides the use of an agent of the invention for the manufacture of a medicament for the treatment of the above-mentioned disorders.

In still a further aspect the invention provides a method for the treatment of disorders linked to metabotropic glutamate receptors, e.g. for the above-mentioned disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The examples which follow further illustrate the invention.

Example 1.

(2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)-glycine

a) 6-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one

A solution of cis-3-phenyl-2-propen-1-yl diazoacetate (1 g, 4.95 mmol) in anhydrous toluene (165 ml) was added to a refluxing solution of bis(N-t-butylsalicylaldiminato)copper (II) (0.104 g, 0.25 mmol) in anhydrous toluene (165 ml) with stirring under an argon atmosphere for 12 hours. After cooling, the reaction mixture was evaporated and the residue subjected to flash chromatography, eluting with petroleum ether containing from 10 to 40% of ethyl acetate, to give the title compound. (0.75 g, 87%), m.p. 112-3°C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.60 (2H, m, 1-CH and 5-CH), 2.78 (1H, t, J=8.8 Hz, 6-CH), 4.05 (1H, dd, J=0.6 Hz, J=9.8 Hz, 4-CH<sub>a</sub>), 4.35 (1H, dt, J=2.7 Hz, J=9.8 Hz, 4-CH<sub>b</sub>), 7.20-7.35 (5H, m, aromatic)

b) 2-Hydroxymethyl-3-phenylcyclopropanecarboxylic acid (4-morpholinyl)amide

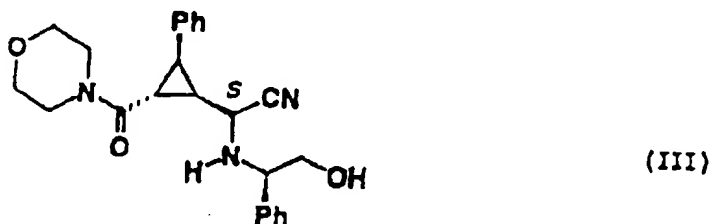
A 2.0 M solution of trimethylaluminium in hexane (22.35 ml) was added dropwise over 20 minutes to a solution of morpholine (3.9 ml) in anhydrous CH<sub>2</sub>Cl<sub>2</sub>,

- (108 ml) with stirring at room temperature under an argon atmosphere. The stirring was continued for 20 minutes after the addition of a solution of the compound obtained in a) (2.59 g, 14.88 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (67 ml) over 20 minutes, and the resulting mixture was then heated at 40°C for 20 hours. The reaction mixture was acidified cautiously with 1N HCl, the organic phase was separated out and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 60 ml). The combined organic phases were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and, after evaporation of the solvent, the residue (3.7 g) was subjected to flash chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ /methanol (95/5) to give the title compound. (3.50 g, 90%), m.p. 103°C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.00 (2H, m, 1-CH and 2-CH), 2.50 (1H, t,  $J=5.5$  Hz, 3-CH), 3.40-3.80 (8H, m, morpholine), 3.90-4.15 (2H, m,  $\text{CH}_2\text{OH}$ ), 7.15-7.40 (5H, m, aromatic)
- c) A solution of the compound obtained in b) (3.40 g, 13.03 mmol) in anhydrous tetrahydrofuran (200 ml) was added dropwise over 30 minutes to a solution of lithium hexamethyldisilazide, prepared by adding a 1.5 M solution of butyllithium in hexane (26 ml) to a solution of anhydrous hexamethyldisilazane (8.3 ml) in tetrahydrofuran (200 ml). The addition was carried out at room temperature under an argon atmosphere. Stirring was continued for 1 hour, after which the reaction mixture was diluted with saturated  $\text{NH}_4\text{Cl}$  (500 ml) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 200 ml). The combined organic extracts were then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give a residue which was subjected to flash chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ /methanol (95/5) to give the epimer of the compound obtained in b). (3.00 g, 88%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.05 (2H, m, 2-CH and OH), 2.25 (1H, t,  $J=5.0$  Hz, 1-CH), 2.85 (1H, dd,  $J=5.0$  Hz,  $J=12.0$  Hz, 3-CH), 3.50-3.90 (8H, m, morpholine ring), 3.85 (2H, dd,  $J=6.7$  Hz,  $J=12.0$  Hz,  $\text{CH}_2\text{OH}$ ), 7.15-7.40 (5H, m, aromatic).

d) 2-Formyl-3-phenylcyclopropanecarboxylic acid  
(4-morpholinyl)amide

PCC (4.20 g, 19.48 mmol) was added to a solution of  
the compound obtained in c) (3.00 g, 11.49 mmol) in  
5 anhydrous  $\text{CH}_2\text{Cl}_2$  (130 ml) and the resulting mixture  
was stirred at room temperature under an argon  
atmosphere for 16 hours. The reaction mixture was  
then diluted with ethyl ether and filtered and the  
solvent was evaporated off. Flash chromatography of  
10 the residue and elution with ethyl acetate/petroleum  
ether (8/2) gave the title compound. (1.90 g, 64%),  
m.p.  $89^\circ\text{C}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.78-2.90 (1H, m, 2-CH),  
3.12 (1H, t,  $J=4.9$  Hz, 1-CH), 3.35 (1H, dd,  
 $J=6.4$  Hz,  $J=9.4$  Hz, 3-CH), 6.60-3.90 (8H), m, mor-  
15 pholine ring, 7.18-7.40 (5H, m, aromatic), 9.20 (1H,  
d,  $J=5.1$  Hz, CHO).

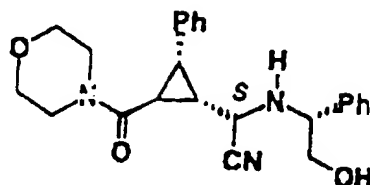
e) R-Phenylglycine (0.45 g, 3.28 mmol) was added to a  
solution of the aldehyde (0.85 g, 3.28 mmol) in  
methanol (32.8 ml) and the resulting mixture was  
20 stirred at room temperature for 2 hours. After  
cooling to  $0^\circ\text{C}$ , TMSCN (0.65 g, 6.56 mmol) was added  
and the resulting mixture was stirred for 12 hours  
at room temperature. Evaporation of the solvent gave  
a residue which was subjected to medium-pressure  
25 chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ /methanol (98/2)  
to give the compound of formula:



(3.00 g, 2%), m.p.  $123-4^\circ\text{C}$   $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.20 (2H,  
m,  $\text{CHCO}$  and  $\text{CH-CHN}$ ), 2.80 (1H, d,  $J=9.6$  Hz,  $\text{CHCN}$ ),  
3.10 (2H, m,  $\text{CHPh}$  and OH), 3.40-3.90 (10H, m, mor-  
30 pholine and  $\text{CH}_2\text{OH}$ ), 3.95 (1H, dd,  $J=3.8$  and  $13.5$  Hz,  
 $\text{CH-CH}_2\text{OH}$ ), 6.70-7.40 (10H, 2 x m, aromatic).

Subsequent elution with the same solvent gave the

compound of formula



(IV)

(0.450 g, 33%), m.p. 146-7°C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.25 (2H, m, CHCO and CH-CHN), 2.60 (1H, d, J=8.0 Hz, CHCN), 2.90 (2H, m, CHPh and OH), 3.50-4.00 (11H, m, morpholine, CH<sub>2</sub>OH and CH-CH<sub>2</sub>OH), 6.90-7.40 (10H, 2 x m, aromatic).

f) (2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)glycine

Lead tetraacetate (0.360 g, 0.81 mmol) was added to a solution of the compound obtained in e), formula (IV) (0.300 g, 0.74 mmol) in an anhydrous methanol/methylene chloride mixture (12 ml, 1/1); after 10 minutes, water (10 ml) was added and the resulting mixture was filtered through Celite. After evaporation of the solvent, the residue was refluxed in 6N HCl (30 ml) for 12 hours. The reaction mixture was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 ml) and evaporated. The residue was subjected to chromatography on an ion exchange resin of Dowex 50 x 2 200 type: elution with 10% pyridine gave the title compound. (0.110 g, 63%), m.p. 221°C; <sup>1</sup>H-NMR (D<sub>2</sub>O+DCI) δ 2.15 (1H, td, J=5.2 and 9.3 Hz, 1'-CH), 2.50' (1H, t, J=5.2 Hz, 2'-CH), 3.05 (1H, dd, J=5.2 and 9.3 Hz, 3'-CH), 3.20 (1H, d, J=10.2 Hz, 2-CH), 7.30 (5H, br s, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 22.90 (C-1'), 27.76 (C-2'), 31.33 (C-3') 51.50 (C-2), 127.66, 128.57, 128.57, 128.94, 133.26 (aromatic), 169.69, 175.27 (CO); [α]<sub>D</sub><sup>20</sup>-108 (c 0.15, 2.5N HCl).

#### Example 2

In a similar manner to Example 1, starting with the appropriate aldehydes of formula (II) and using, depending on the case, R- or S-α-phenylglycinol as

indicated in the above schemes 1-4, the following compounds were obtained:

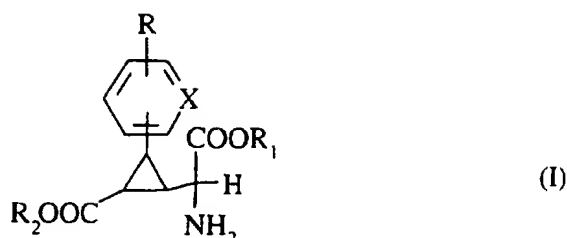
- (2R,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 86% yield; m.p. 240-1°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.95 (1H, td, J=5.4, 8.9 and 10.8 Hz, 1'-CH), 2.55 (1H, t, J=5.4 Hz, 2'-CH), 2.85 (1H, dd, J=5.4 and 8.9 Hz, 3'-CH), 3.00 (1H, d, J=10.8 Hz, 2-CH), 7.20-7.35 (5H, m, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 23.90, 27.78, 29.97, 50.40, 128.03, 128.43, 129, 17, 132.76, 170.81, 175.24; [α]<sub>D</sub><sup>20</sup> -74 (c 0.30, 2.5N HCl).
- (2R,1'R,2'R,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 74% yield; m.p. 221-3°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 2.10 (1H, dt, J=5.0 and 10.5 Hz, 1'-CH), 2.40 (1H, t, J=5.0 Hz, 2'-CH), 3.00 (2H, m, 3'-CH and 2-CH), 7.30 (5H, d, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 22.91, 27.83, 31.39, 51.49, 127.69, 128.59, 128.96, 133.28, 169.70, 175.25; [α]<sub>D</sub><sup>20</sup> +100 (c 0.20, 2.5N HCl).
- (2S,1'R,2'R,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 70% yield; [α]<sub>D</sub><sup>20</sup> +72 (c 0.30, 2.5N HCl).
- (2R,1'R,2'S,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 48% yield; m.p. 219-220°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.80 (1H, dt, J=9.4 and 11.9 Hz, 1'-CH), 2.49 (1H, t, J=9.4 Hz, 2'-CH), 2.75 (1H, t, J=9.4 Hz, 3'-CH), 4.10 (1H, d, J=11.9 Hz, 2-CH), 7.10-7.30 (5H, m, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 23.99, 24.54, 28.51, 49.00, 127.86, 129.20, 129.71, 133.33, 171.27, 175.24; [α]<sub>D</sub><sup>20</sup> +20 (c 0.50, 2.5N HCl).
- (2R,1'S,2'R,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 53% yield; m.p. 219-220°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.90 (1H, dt, J=8.8 and 11.5 Hz, 1'-CH), 2.55 (1H, t, J=8.8 Hz, 2'-CH), 2.80 (1H, t, J=8.8 Hz, 3'-CH), 4.15 (1H, d, J=11.5 Hz, 2-CH), 7.10-7.30 (5H, m, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 23.46, 24.20, 28.54, 49.16, 127.61, 128.95, 129.49, 132.94, 171.05, 173.98; [α]<sub>D</sub><sup>20</sup> -17 (c 0.60, 2.5N HCl).
- (2S,1'S,2'R,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 48% yield; [α]<sub>D</sub><sup>20</sup> -21 (c 0.50, 2.5N HCl).
- (2S,1'R,2'S,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 55% yield; [α]<sub>D</sub><sup>20</sup> +18 (c 0.40, 2.5N HCl).

(2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-o-methoxyphenyl-cyclopropyl)glycine.

(0.100 g, 82%), m.p. 219-20°C; <sup>1</sup>H-NMR (D<sub>2</sub>O+DCI) δ 2.15 (1H, td, J=5.8 and 10.3 Hz, 1'-CH), 2.40 (1H, t, J=5.8 Hz, 2'-CH), 2.9-3.10 (2H, m, 3'-CH and 2-CH), 3.80 (3H, s, OMe), 6.90-7.40 (4H, m, aromatic); [α]<sub>D</sub><sup>20</sup> -81 (c 0.15, 2.5N HCl).

## CLAIMS

1. A compound of formula I



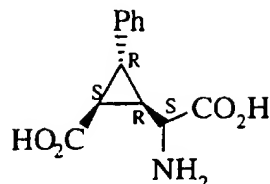
wherein

- R is hydrogen, halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl, C<sub>1</sub>-C<sub>4</sub>haloalkoxy, cyano, nitro, -COOR<sub>1</sub> (R<sub>1</sub> being as defined below), -CONR<sub>3</sub>R<sub>4</sub> (R<sub>3</sub> and R<sub>4</sub> independently being hydrogen or C<sub>1</sub>-C<sub>4</sub>alkyl), -PO(OR<sub>1</sub>)<sub>2</sub> (R<sub>1</sub> being as defined below), -SO<sub>3</sub>R<sub>1</sub> (R<sub>1</sub> being as defined below) or -NH-CO-R<sub>5</sub> (R<sub>5</sub> being C<sub>1</sub>-C<sub>4</sub>alkyl or phenyl), R<sub>1</sub> and R<sub>2</sub>, independently, are hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl or benzyl, and

- X is =CH-, =N- or  $\begin{array}{c} \text{O}^- \\ | \\ \text{N}^+ \end{array}$  or a salt thereof.

2. A compound of formula I according to claim 1 wherein R is hydrogen, an halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl or C<sub>1</sub>-C<sub>4</sub>haloalkoxy, R<sub>1</sub> and R<sub>2</sub> are hydrogen and X is =CH- or =N- in ortho position to the bond which is linked to the cyclopropyl moiety, or a salt thereof.
3. A compound of claim 1 wherein R is hydrogen or C<sub>1</sub>-C<sub>4</sub>alkyl, R<sub>1</sub> and R<sub>2</sub> are hydrogen and X is =CH-.

4. The compound of formula



and its salts.

5. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use as a pharmaceutical.
6. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use in disorders linked to metabotropic glutamate receptors.
7. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use in the treatment of cerebral ischemia, head trauma, subarachnoid haemorrhage, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, Parkinson syndrome, convulsive disorders, muscular spasms, pain, cognitive disorders, schizophrenia, anxiety, emesis and drug abuse.
8. A pharmaceutical composition comprising a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.
9. The use of a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, as a pharmaceutical for the treatment of disorders linked to metabotropic glutamate receptors.



10. The use of a compound of anyone of claims 1 to 4 in  
free or pharmaceutically acceptable salt form, for  
the manufacture of a medicament for the treatment of  
disorders linked to metabotropic glutamate  
5 receptors.
11. A method for the treatment of disorders linked to  
metabotropic glutamate receptors in a subject in  
need of such treatment, which comprises  
administering to such subject a therapeutically  
10 effective amount of a compound of anyone of claims  
1 to 4 in free or pharmaceutically acceptable salt  
form.

## INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/EP 96/05079A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C229/48 A61K31/195 C07D213/55

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BIOORG. MED. CHEM. LETT. (1996), 6(18), 2243-2246 CODEN: BMCLE8; ISSN: 0960-894X, 1996, XP000617002 MARINOZZI, MAURA ET AL: "Asymmetric synthesis of enantiomerically pure (2S,1'S,2'S,3'R)- phenylcarboxycyclopropylglycine (PCCG-4): a potent and selective ligand at group II metabotropic glutamate receptors" see the whole document --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

30 January 1997

Date of mailing of the international search report

10.02.97

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Information on patent family members

International Application No

PCT/EP 96/05079

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EP-A-0363994	18-04-90	JP-A- 2108654 DE-D- 68909362 DE-T- 68909362 ES-T- 2059669 US-A- 5068412	20-04-90 28-10-93 10-03-94 16-11-94 26-11-91